(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 218 433**
A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **86307441.5**

(22) Date of filing: **29.09.86**

(51) Int. Cl.⁴: **A 61 K 31/48**, C 07 D 457/04

(30) Priority: **01.10.85 US 782338**

(43) Date of publication of application: **15.04.87 Bulletin 87/16**

(84) Designated Contracting States: **BE CH DE FR GB IT LI LU NL SE**

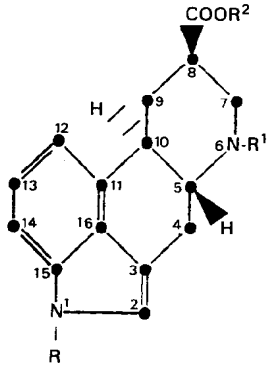
(71) Applicant: **ELI LILLY AND COMPANY, Lilly Corporate Center, Indianapolis Indiana 46285 (US)**

(72) Inventor: **Cohen, Marlene Lois, 521 Oakwood Drive, Indianapolis Indiana 46260 (US)**
Inventor: **Fuller, Ray Ward, 7844 Singleton Drive, Indianapolis Indiana 46227 (US)**
Inventor: **Garbrecht, William Lee, 7303 Wood Stream Drive, Indianapolis Indiana 46254 (US)**
Inventor: **Whitten, Kathleen Rose, 9302 East 180 South, Zionsville Indiana 46077 (US)**

(74) Representative: **Hudson, Christopher Mark et al, Erl Wood Manor, Windlesham Surrey GU20 6PH (GB)**

(54) Selective method for blocking 5HT2 receptors.

(57) Method of blocking $5HT_2$ without effect on alpha receptors with 1-loweralkyl-6-straight chain alkyl-8β-hydroxycycloalkyloxycarbonylergolines of the formula



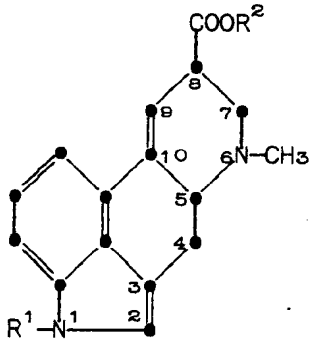
(III)

wherein R is primary or secondary C_1-C_8 alkyl, CH_2C_2-C_4 alkenyl, C_3-C_8 cycloalkyl or C_3-C_6 cycloalkyl-substituted C_1-C_5 primary or secondary alkyl, the total number of carbon atoms in R not to exceed 8; R^1 is C_1-C_4 straight chain alkyl or allyl, and R^2 is hydroxy C_5-C_7 cycloalkyl, or a pharmaceutically-acceptable salt thereof.

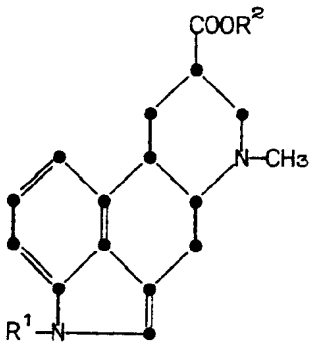
EP 0 218 433 A1

SELECTIVE METHOD FOR BLOCKING $5HT_2$ RECEPTORS

United States Patent No. 3,580,916 discloses a group of lysergic and 9,10-dihydrolysergic acid esters formed with various open chain and cyclic diols of the following structures:



and

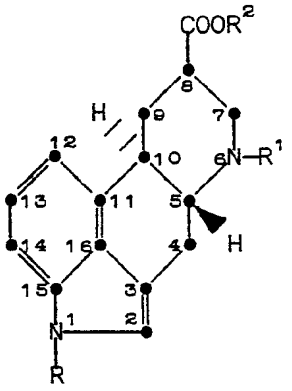


(I) (II)

wherein R^2 is H, C_1-C_3 alkyl, allyl or benzyl and R^2 is C_2-C_8 monohydroxyalkyl, C_2-C_8 dihydroxyalkyl or C_5-C_{11} monohydroxycycloalkyl having from 5-8 ring carbons. The compounds were described as being neurosedative agents in non-human animals.

The R^2 group in (I) or (II) when it is hydroxycycloalkyl is formed by the reaction of a dihydroxycycloalkane with an "activated" form of lysergic or dihydrolysergic acid.

This invention provides an ergoline of Formula (III):



(III)

for use in blocking $5HT_2$ receptors without effect on alpha receptors, wherein R is primary or secondary C_1-C_8 alkyl, CH_2-C_2-C_4 alkenyl, C_3-C_8 cycloalkyl or C_3-C_6 cycloalkyl-substituted C_1-C_5 primary or secondary alkyl, the total number of carbon atoms in R not to exceed 8; R^1 is allyl or C_1-C_4 straight-chain alkyl; ie; methyl, ethyl, n-propyl or n-butyl; and R^2 is hydroxy-substituted C_5-C_7 cycloalkyl, and pharmaceutically-acceptable acid addition salts thereof.

Groups which R in the above formula represent include methyl, ethyl, allyl, n-propyl, isopropyl, crotyl, methallyl, n-hexyl, sec-amyl, sec-octyl, n-heptyl, 2,4-dimethylpentyl, 2-ethylpentyl, cyclopropyl, cyclopropylmethyl, cyclopentyl methyl, 2-cyclobutyl ethyl, cyclohexyl, isobutyl, sec.-butyl, 3-methyl-2-butyl isoamyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl(isohexyl), 2-hexyl, 3-hexyl n-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, n-octyl, 2-octyl, 3-octyl, 4-octyl isooctyl, 2-methylheptyl, 3-methyl-2-heptyl, and

the like. Illustrative of the groups which R^2 represents include 4-hydroxycyclohexyl, 3-hydroxycyclohexyl, 3-hydroxycyclopentyl, 3-hydroxycycloheptyl, 4-hydroxycycloheptyl, 2-hydroxycyclopentyl, 2-hydroxycyclohexyl, 2-hydroxycycloheptyl and the like.

Compounds according to the above Formula (III) can be named as ergoline derivatives in which the trans(-) or 5R,10R configuration of the bridgehead hydrogens is specified (The same configuration as in the naturally-occurring ergot alkaloids). In United States patent 3,580,916, a different naming system was used; the basic ring system is a 6aR,10aR-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinoline. The trivial name "ergoline" is used herein with the numbering system specified in (III) above when R^1 is other than methyl. When R^1 is methyl, the 9,10-dihydrolysergic acid nomenclature is used. Illustratively, 9,10-dihydrolysergic acid is 6aR,10aR-7-methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinoline-9β-carboxylic acid or 6-methyl-8β-carboxyergoline.

Pharmaceutically-acceptable acid addition salts of the compounds of Formula (III) useful in the process of this invention include salts derived from non-toxic inorganic acids such as: hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, hydrobromic acid, hydriodic acid, phosphorous acid and the like, as well as salts derived from non-toxic organic acids such as aliphatic mono and dicarboxylic acids, phenyl-substituted alkanoic acids, and alkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids,

etc. Such pharmaceutically-acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, fluoride, acetate, propionate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methoxybenzoate, phthalate, terephthalate, benzenesulfonate, toluenesulfonate, chlorobenzenesulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenyl-butyrate, citrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate and the like salts.

Those useful in the therapeutic processes of this invention include:

2-Hydroxycyclohexyl 1-methyl-8β-9,10-dihydrolysergate succinate

2-Hydroxycyclopentyl 1,6-diethylergoline-8β-carboxylate hydrochloride

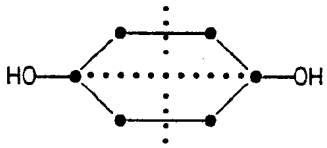
2-Hydroxycycloheptylergoline 1-n-propyl-6-allyl-8β-carboxylate sulfate

2-Hydroxycyclohexyl 1-isopropyl-6-n-propyl-ergoline-8β-carboxylate hydrobromide

4-Hydroxycycloheptyl 1-allyl-6-ethylergoline-8β-carboxylate tartrate and the like.

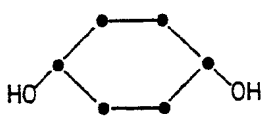
While the configuration at asymmetric carbons 5,8 and 10 in Formula (III) is set (5β,8β and 10α), the cycloalkane diols each have two additional asymmetric

carbons. For example, cyclohexane-1,3-diol should exist as two racemates, each racemate containing two enantiomers or stereoisomers. However, it is possible to draw a plane of symmetry through the cis isomer of the molecule (C-2 to C-5), thus producing a meso form in which two of the isomers are superimposable. Thus, certain of the diols used to lower the esters of this invention exist as a racemate and a meso form. However, when an optically-active group is attached to one of the hydroxyls, such as a dihydrolysergic acid group, to form an ester, a plane of symmetry can no longer be drawn and the mono esters of cyclopentanediols, cyclohexanediols and cycloheptanediols will ordinarily each exist as two (±) diastereoisomeric pairs. However, with certain diols such as cyclohexane-1,4-diol, two planes of symmetry can be drawn, indicated by the dotted lines in Formula (IV)



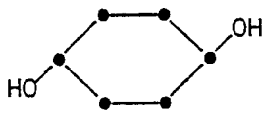
(IV)

and the compounds exist as two meso forms; ie, both sets of mirror images are superimposable. However, two geometric isomers exist designated as the cis form and the trans form drawn for convenience in two dimensions as (IVa) and (IVb).



cis

(IVa)



trans

(IVb)

When monoesters with 9,10-dihydrolysergic acid are formed, although each ester could theoretically exist in two diastereoisomeric forms, an inspection of the models indicates that such is not the case and that only two non optically-active esters exist. These will be named as the cis or trans isomer. (For a more detailed explanation of the stereochemistry of cycloalkane-1,4-diols, see "Conformational Theory" by Michael Hanach. (Academic Press, Inc., Fifth Avenue, New York, N.Y. 10003, 1965).

The preparation of compounds represented by Formula (III) above is detailed in United States Patent No. 3,580,916.

According to this procedure, dihydrolysergic acid is first alkylated in the indole nitrogen using standard procedures, for example, base plus an alkyl halide. Liquid ammonia is a convenient solvent with sodamide as the base and methyl, ethyl, isopropyl or n-propyl iodide or allyl chloride or bromide as the alkylating agent. (See United States Patent

3,183,234-Garbrecht and Lin which contains general directions and a specific example of this alkylation procedure).

Alternatively, the procedure of Marzoni, U.S. Serial No. 782,339, can be used, whereby 9,10-dihydrolysergic acid is reacted with an aryl sulfonate, R-O-SO_2-phenyl-Y where R has its previous meaning and Y is CH_3, NO_2 or Br, in the presence of an alkali metal hydroxide in an aprotic solvent, conveniently NaOH in DMF, to yield the desired N-1 derivative.

With the indole nitrogen substituent in place, if 9,10-dihydrolysergic acid was the starting material, the next step in the synthetic procedure is esterification. This procedure requires heating; ie, preferably at about 120°C, but the reaction is an otherwise standard acid-catalyzed esterification. The free acid prepared above and cycloalkanediol are used and the work-up of the esterification mixture involves partioning between water and a water-immiscible solvent; (CH_2Cl_2)for example.

If it is desired to prepare a product in which the 6-methyl of the dihydrolysergic acid series is replaced by ethyl, n-propyl, n-butyl or allyl, the replacement of the 6-methyl group must take place after N^1-alkylation, using an ester (preferably a C_1-C_2 lower allyl ester as the substrate. Replacement of the 6-methyl with ethyl, n-propyl, alkyl, n-butyl or the like, can conveniently be carried out by the procedure of Kornfeld and Bach, United States Patent 4,166,182,

whereby the N-methyl is reacted with cyanogen bromide to form an N-cyano derivative. The cyano group is removed by hydrogenation using zinc dust and hydrochloric acid. The resulting product is an N^1-alkylergoline-8β-carboxylic acid which is a secondary amine. The desired ester group is now prepared, using the standard reaction conditions with an alcohol of formula R^2OH. The secondary amine can then be alkylated or allylated in DMF solution in the presence of a base such as sodium carbonate to form a 1-alkyl (or allyl)-6-substituted ergoline-8β-carboxylic acid ester. It might seem redundant to realkylate the above secondary amine with methyl iodide since the N-methyl group was present in the starting material. It should be pointed out, however, that a methyl group containing isotopic or radioactive C or H could be inserted to give a derivative useful in metabolic studies.

The preparation of the 4-hydroxycyclohexyl ester of 1-isopropyl-6-methylergoline-8β-carboxylic acid and of its cis-(±) and trans-(±) racemates is illustrated below.

Example 1

Preparation of 4-Hydroxycyclohexyl 1-Isopropyl-9,10-dihydrolysergate

A reaction mixture was prepared from 9.36 g of 1-isopropyl-9,10-dihydrolysergic acid, 20 g of cyclohexane-1,4-diol and 5.7 g of p-toluenesulfonic acid.

The reaction mixture was heated overnight at about 90°C and was then cooled. The reaction mixture was partitioned between 400 ml of methylene dichloride and 250 ml of water, the pH being adjusted to about 11 with concentrated ammonium hydroxide. The organic layer was washed with 200 ml of 10% hydrochloric acid followed by 200 ml of water. The organic layer was separated and evaporated to dryness in vacuo, to leave 4-hydroxycyclohexyl 1-isopropyl-9,10-dihydrolysergate hydrochloride formed in the above reaction and workup, as a residue. The hydrochloride salt crystallized and the crystalline salt was separated by filtration: yield = about 2.3 g (17%); nmr indicated it was a mixture of cis and trans isomers; molecular ion of free base at 410.

Following the above procedure 3.12 g of 1-isopropyl-9,10-dihydrolysergic acid, 4.64 g of purified trans-cyclohexane-1,4-diol and 1.9 g of p-toluene sulfonic acid were heated together at 110°C overnight. The reaction mixture was cooled and the cooled mixture partitioned between the ethylene dichloride and water at pH = about 10. The organic layer was separated and the separated layer washed with 250 ml of 10% hydrochloric acid. The hydrochloric acid salt was recovered by filtration, but crystallized with difficulty from a methanol/ether solvent mixture. The organic filtrate was concentrated, and the residue dissolved in ethylene dichloride. The hydrochloride salt fractions were combined in aqueous solution, which was contacted with dilute ammonium hydroxide to convert the hydrochloride salt to the free base. The free base was extracted into

$(CH_2Cl)_2$ and purified. The free base was then converted to the maleate salt of trans-4-hydroxycyclohexyl 1-isopropyl-9,10-dihydrolysergate which was recrystallized from an ethanol/ether solvent mixture; molecular ion at 410; yield = 0.43 g.

Analysis: Calc.: C, 66.14; H, 7.27; N, 5.23;
Found: C, 65.98; H, 7.06; N, 5.17.

Following the above procedure, 3.12 g of 1-isopropyl-9,10-dihydrolysergic acid and 5.5 g of cis-cyclohexane-1,4-diol were reacted in the presence of 1.9 g of p-toluenesulfonic acid by heating at about 90°C for 18 hours. The reaction mixture was worked up as above and the solvent evaporated to dryness to yield the free base of cis-(±)-4-hydroxycyclohexyl 1-isopropyl-9,10-dihydrolysergate. The free base was converted to the maleate salt and the maleate salt crystallized from a mixture of methanol and ether to yield a tan colored solid. Two more recrystallizations followed by a charcoal decolorization yielded 1.3 g of cis-4-hydroxy-cyclohexyl-1-isopropyl-9,10-dihydrolysergate maleate; yield = 1.3 g; molecular ion at 410.

The intermediates cis and trans-cyclohexane-1,4-diols were prepared as follows:

Preparation I

A reaction mixture containing 23.2 g of cyclohexane-1,4-diol (estimated to be a 50/50 mixture of the cis and trans isomers) and 20.4 g of n-butyl-boronic

acid was prepared in 300 ml of toluene. The reaction mixture was heated to reflux temperature overnight using a Dean-Stark trap. The reaction mixture was concentrated in vacuo to give a mixture of the cis isomer as the boronic acid ester and the unreacted trans isomer. The cis conformation only of the two cyclohexane-1,4-diols will form a diester with n-butylboronic acid. The trans isomer will not react because the resulting diester would be too strained to form a five-membered ring. The n-butyl boronic ester distilled at 65-74°C at 0.1 torr. 10 ml of ethylene glycol were added to the distillate which was heated at about 80°C for an hour to displace the boronic ester grouping from the cis-cyclohexane-1,4-diol. The n-butylboronic ethylene glycol ester with ester was removed by distillation at 35-80°C at 3-8 torr. The residue comprising cis-cyclohexane-1,4-diol was recrystallized from ethyl acetate. Yield = 1.44 g.

The structure was confirmed by 360 MH_z nmr.

The trans-isomer was prepared by adding 10 ml of ethylene glycol to the residue remaining after distillation of the boronic ester cis isomer. The mixture was allowed to sit for about 1 hour at which time the boronic ester of ethylene glycol was removed by distillation at about 35°C at 3 torr. The hot residue consisting of trans-cyclohexane-1,4-diol was recrystallized from ethyl acetate; yield = 5.2 g. Again, the trans structure was confirmed by 360 MH_z nmr.

The novel use of the invention whereby $5HT_2$ receptors are blocked but alpha receptors are not

affected at a given dose level is potentially useful in treating disease states in which an excess of circulating serotonin is a major cause. These disease states include hypertension, thrombosis, anorexia nervosa, depression, mania, carcinoid syndrome, migraine and vasospasm. The lack of alpha receptor inhibitory activity indicates that the usual undesirable side affects associated with alpha receptor blockade -- postural hypotension, tachycardia, impotence, and increased plasma renin levels-- will not accompany the use of a compound according to Formula (III) in treating hypertension, etc. in contrast to many presently available hypotensive agents including ketanserin.

Compounds according to Formula (III) have an extremely high affinity for $5HT_2$ receptors, with a much lower affinity for alpha receptors. Ratios of relative dissociation constants for interaction with alpha to $5HT_2$ receptors are of the order of 200,000-300,000 indicating dramatic selectivity for $5HT_2$ receptors. The apparent dissociation constants (K_B) are a measure of affinity for $5HT_2$ and alpha receptors and are expressed as the negative logarithm and are determined according to the following protocol.

Male Wistar rats (150-300 gram weight) were killed and their external jugular veins and thoracic aortas dissected free of connective tissue, cannulated in situ and placed in a modified Krebs' bicarbonate buffer in a suitable tissue bath. Two L-shaped 30-gauge stainless-steel hypodermic needles were inserted in each cannula and the dissected vessels gently pushed onto the

needles. One needle was attached with thread to a stationary glass rod and the other to the transducer. [The procedure employed was that described by Hooker, Calkins and Fleisch, Blood Vessels, 14, 1, (1977) for use with circular smooth muscle preparations.]

The modified Krebs' bicarbonate buffer had the following makeup: (concentrations in millimoles): sodium chloride, 118.2; potassium chloride, 4.6; calcium chloride dihydrate, 1.6; potassium dihydrogenphosphate, 1.2; magnesium sulfate, 1.2; dextrose, 10.0; sodium bicarbonate, 24.8; and water q.s. to 1000 g. The tissue baths were maintained at 37°C and were aerated with 95% oxygen-5% CO_2. An initial optimum resting force of 1 and 4 g was applied to the jugular vein and aorta, respectively. Isometric contractions were recorded as changes in grams of force on a Beckman Dynograph with Statham UC-3 transducers and microscale accessory attachment. Tissues were allowed to equilibrate 1 to 2 hours before exposure to drugs. Control responses to serotonin in the jugular vein and to norepinephrine in the aorta were obtained. The vessels were then incubated with appropriate concentrations of antagonist for one hour. Responses to serotonin or to norepinephrine were then repeated in the presence of the antagonist. Contraction to serotonin was evaluated in the jugular vein since this tissue produces marked responses to serotonin in the absence of alpha receptors -- see Cohen and Wiley, J. Pharm. Exp. Ther., 205, 400 (1978) and Cohen, Colbert and Wittenauer, Drug Dev. Res., 5 513 (1985) for descriptions of the procedures

employed. Alpha receptor antagonist activity was evaluated in the aorta (α_1) or guinea pig ileum (α_2).

Apparent antagonist dissociation constants were determined for each concentration of antagonist according to the following equation:

$$K_B = \frac{[B]}{[\text{dose ratio}-1]}$$

wherein [B] is the concentration of the antagonist and the dose ratio is the ED_{50} of the agonist in the presence of the antagonist divided by the control ED_{50}. These results are then expressed as the negative logarithm of K_B. The -log K_B values obtained for 4-hydroxycyclohexyl 1-isopropyl-9,10-dihydrolysergate, isomer mixture (racemate) and pure isomers (cis and trans referring to stereochemistry of the hydroxycyclohexyl group) plus standard error against $5HT_2$ receptors are given below in Table 1.

Table 1

Compound	-Log K_b ± S.E.
4-hydroxycyclohexyl 1-isopropyl-9,10-dihydrolysergate	
mixture	10.18 (±) 0.12
cis	9.95 (±) 0.13
trans	10.02 (±) 0.07

The lack of alpha blocking activity for compounds of Formula (III) was demonstrated by the following

experiment. The in vitro rat aorta preparation described above was used for α_1-receptors and the guinea pig ileum for α_2-receptors. ED_{50} (median effective dose) for norepinephrine was determined in the presence of a 10^{-5} molar dose of the test compound and this ED_{50} compared to a control ED_{50} The resulting dissociation constants are given in Table 2 below.

Table 2

Compound	-Log K_b ± S.E.	
4-hydroxycyclohexyl 1-isopropyl-9,10-dihydro-lysergate	α_1	α_2
mixture	4.84 ± 0.34	6.93 ± 0.22
cis	5.35 ± 0.33	6.81 ± 0.08
trans	5.71 ± 0.17	7.18 ± 0.18

None of the above compounds significantly antagonized alpha receptors at a 10^{-6} M. dose.

The compounds of this invention also lack demonstrable effects against histamine or carbamyl choline (muscarinic) contraction in guinea pig trachea, using standard procedures.

Table 3

Compound	-Log K_b ± S.E.	
4-hydroxycyclohexyl 1-isopropyl-9,10-dihydrolysergate	Histamine	Muscarinic
Mixture	<5	<5
trans	<5	<5

The specificity for $5HT_2$ receptors compared to $5HT_1$, receptors of compounds according to Formula (III) above in rat cortical membranes is given in Table 4. The procedures employed are those set forth in Cohen, Colbert and Wittenauer (loc. cit.) for other tissues.

Table 4

Compound	Rat Cortical Membrane Binding IC_{50} (nM)	
4-hydroxycyclohexyl 1-isopropyl-9,10-dihydrolysergate	$5HT_1$	$5HT_2$
mixture	530	3
trans	390	0.7

In spontaneously hypertensive rats (SHR), in which blockade of $alpha_1$ receptors but not $5HT_2$ receptors lowers blood pressure, there was no effect on blood pressure or heart rate upon oral administration of 4-hydroxycyclohexyl 1-isopropyl-9,10-dihydrolysergate at a 10 mg/kg dose.

The relative potency and selectivity of the cis and trans isomers and cis-trans isomer mixture of 4-hydroxycyclohexyl 1-isopropyl-9,10-dihydrolysergate for $5HT_2$ and $alpha_2$ receptors was demonstrated in vivo in pithed SHR according to the following protocol.

SHR were anesthesized with halothane, femoral arterial and venous catheters were implanted as before and the trachea was cannulated. Each rat was pithed by passing a steel rod through the right orbit and down the entire length of the spinal column. The steel rod remained in place for the duration of the experiment. Immediately after pithing, the rats were ventilated with room air. An equilibration period of 15 minutes was observed prior to control measurements and administration of drugs or vehicle p.o. Increasing doses of serotonin or the $alpha_2$ agonist clonidine were injected i.v. one or six hours after oral treatment with the agonists. The response was recorded and the blood pressure allowed to recover to control levels after serotonin. Cumulative dose-response curves to clonidine were determined. The test drug solution was prepared fresh daily. Tables 5 and 6 give the results of these determinations at a dose level of 0.1 mg/kg.

Table 5 Relative Potency of Serotonin (5HT) Antagonists One Hour After Oral Administration of 0.1 mg/kg to Pithed Rats[a]

Compound	5HT Dose, mg/kg, iv[b]	Curve Shift Relative to trans
trans	4000	--
mixture	1100	3.6
cis	345	11.6
Vehicle	9	444.4

[a]Conscious spontaneously hypertensive rats (SHR) were treated orally 1 hour before anesthesia, pithing and determination of pressor-dose response curves to multiple doses of 5HT iv (n=4-10/group).

[b]Dose of 5HT required to increase mean arterial blood pressure by 50 mmHg.

Table 6 Relative Potency of Serotonin (5HT) Antagonists Six Hours After Oral Administration of 0.1 mg/kg to Pithed Rats[a]

Compound	5HT Dose, mg/kg, iv[b]	Curve Shift Relative to trans
trans	680	--
mixture	123	5.5
cis	28	24.3
Vehicle	9	75.6

[a]Conscious spontaneously hypertensive rats (SHR) were treated orally 6 hours before anesthesia, pithing and determination of pressor-dose response curves to multiple doses of 5HT iv (n=4-10/group).

[b]Dose of 5HT required to increase mean arterial blood pressure by 50 mmHg.

When a dose of 0.3 mg/kg po of cis-4-hydroxy-cyclohexyl 1-isopropyl-9,10-dihydrolysergate was given, the dose of 5HT required to increase mean arterial BP by

50 mmHg was 1800, giving a curve shift of 6.7. When a dose of 0.03 mg/kg po of trans-4-hydroxycyclohexyl 1-isopropyl-9,10-dihydrolysergate was given, the 5HT dose required to shift mean arterial BP 50 mmHg was 200 μg/kg, iv, indicating by extrapolation, that the trans isomer was 3X the cis isomer in potency.

The above differences in potency between the cis and trans isomers of 4-hydroxy cyclohexyl 1-isopropyl-9,10-dihydrolysergate when administered by the oral route were unexpected considering the in vitro date of Table 1 above.

The alpha$_2$ antagonist activity as determined in pithed 5HR at a 100 mg/kg dose level po was slight for the isomer mixture and the individual isomers and showed a greater specificity (5HT$_2$ vs alpha$_2$) than the in vitro date of Table 1-2 indicated.

In humans and mammals other than SHR, hypertension may be mediated through 5HT$_2$ receptors. Thus, compounds of Formula (III) would be expected to lower blood pressure in humans as does ketanserin, another 5HT$_2$ blocker, but without the side effects attributable to alpha adrenergic receptor blockade.

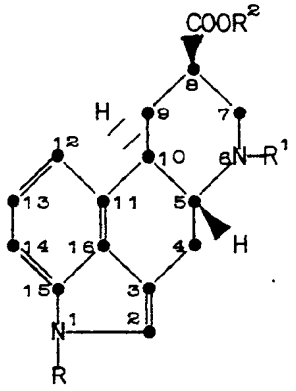
In carrying out our novel therapeutic process, a pharmaceutically-acceptable salt of a drug according to Formula (III) above formed with a non-toxic acid is administered orally or parenterally to a mammal with an excess of circulatory serotonin in which it is desirable to block 5HT$_2$ receptors in order to alleviate symptoms attributable to excessive serotonin levels such as high blood pressure and migraines. For parenteral

administration, a water soluble salt of the drug is dissolved in an isotonic salt solution and administered by the i.v. route. For oral administration, a pharmaceutically-acceptable salt of the drug is mixed with standard pharmaceutical excipients such as starch and loaded into capsules or made into tablets, each containing 0.1 to 100 mg of active drug. Dosage levels of from 0.1-10 mg/kg have been found to be effective in blocking $5HT_2$ receptors. Thus, the oral dosage would be administered 2-4 times per day, giving a daily dosage range of about .003 to about 10.0 mg./kg. per day.

Other oral dosage forms, suspensions, elixirs and tablets, can also be utilized and are preparable by standard procedures.

CLAIMS

1. Use of an ergoline of Formula (III):



(III)

wherein R is primary or secondary C_1-C_8 alkyl, CH_2C_2-C_4 alkenyl, C_3-C_8 cycloalkyl or C_3-C_6 cycloalkyl-substituted C_1-C_5 primary or secondary alkyl, the total number of carbon atoms in R not to exceed 8; R^1 is C_1-C_4 straight chain alkyl or allyl, and R^2 is hydroxy C_5-C_7 cycloalkyl, or a pharmaceutically-acceptable salt thereof, for the manufacture of a medicament useful in blocking $5HT_2$ receptors in humans without effect on alpha receptors.

2. Use of an ergoline of Formula (III), as defined in claim 1, or a pharmaceutically-acceptable salt thereof, for the manufacture of a medicament useful in treating hypertension.

3. Use of an ergoline of Formula (III), as defined in claim 1, or a pharmaceutically-acceptable salt thereof, for the manufacture of a medicament useful for the treatment of migraine.

4. Use of an ergoline of Formula (III), as defined in claim 1, or a pharmaceutically-acceptable salt thereof, for the manufacture of a medicament useful for the treatment of carcinoid syndrome.

5. Use of an ergoline of Formula (III), as defined in claim 1, or a pharmaceutically-acceptable salt thereof, for the manufacture of a medicament useful for the treatment of vasospasm.

6. Use of an ergoline of Formula (III), as defined in claim 1, or a pharmaceutically-acceptable salt thereof, for the manufacture of a medicament useful for the treatment of anorexia nervosa.

7. Use of an ergoline of Formula (III), as defined in claim 1, or a pharmaceutically-acceptable salt thereof, for the manufacture of a medicament useful for the treatment of depression.

8. Use of an ergoline of Formula (III), as defined in claim 1, or a pharmaceutically-acceptable salt thereof, for the manufacture of a medicament useful for the treatment of a mania episode.

European Patent Office

EUROPEAN SEARCH REPORT

0218433
Application number

DOCUMENTS CONSIDERED TO BE RELEVANT

EP 86307441.5

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl 4)
Y	EP - A1 - 0 122 044 (ELI LILLY AND COMPANY) * Abstract; claims 1,4-10 *	1-8	A 61 K 31/48 C 07 D 457/04
Y	CH - A - 549 571 (ELI LILLY AND COMPANY) * Column 1, lines 9-58, formula I; column 2, lines 32-34 *	1-8	
D,A	US - A - 3 580 916 (W.L. GARBRECHT) * Abstract; claim 1, column 5, lines 13-23 *	1-8	
A	EP - A1 - 0 000 533 (LEK) * Abstract; formula I *	1-8	TECHNICAL FIELDS SEARCHED (Int. Cl 4) A 61 K 31/00 C 07 D 457/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	02-12-1986	MAZZUCCO

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO Form 1503 03 82